Applicants propose to amend the claims in order to more particularly point out and distinctly claim the invention. Thus, in claims 6 and 10, subject matter beyond the scope of independent claim 28 has been deleted. In claims 28 and 29 "coemulsifier of the polyoxyethylene type" has been replaced by "polyoxyethylene coemulsifier" as the examiner suggests. No new matter has been added.

Applicants note with appreciation a telephonic interview wherein the examiner confirmed that applicant's remarks concerning Owen were persuasive and that all prior grounds of rejection had been withdrawn.

Claims 2, 6, 10, 15-21, 24 and 28-29 are now finally rejected under 35 U.S.C. § 103(a) as being unpatentable over Weder et al., U.S. Patent 5,997,888 in view of WO 96/37192.

The examiner asserts that Weder et al. discloses cosmetic compositions containing nanodispersions comprising a fatty acid ester of a polyoxyethylene sorbitan, a phospholipid, 0.65% (also 0.867%) of ethanol, a water phase, and a lipophilic active agent such as tocopherol acetate (vitamin E acetate) or vitamin A palmitate, and conventional mixing methods (e.g. utilizing magnetic stirring bars - see col. 8, lines 2-5).

The examiner admits that Weder et al. does not use a combination of a triglyceride and the lipophilic active agent. But the examiner relies on WO 96/37192 to show that the use of a triglyceride to improve stability and solubility of a lipophilic drug in an aqueous emulsion system is conventional. The examiner asserts that the claimed pharmaceutical compositions and process to make them are therefore rendered obvious by the teachings of Weder et al. in view of WO 96/37192.

As noted *supra*, the Weder reference discloses cosmetic nanodispersions which do not comprise the combination of a triglyceride and the lipophilic active ingredient. Therefore, the examiner is respectfully requested to consider the accompanying declaration of Dr. Andreas Supersaxo, an expert in the area of drug delivery systems, who is the first-named inventor of the present application. Dr. Supersaxo compared the nanodispersions of the present invention to those of the closest prior art (Weder).

The results in Table 1 and the accompanying photographs clearly show that the triglyceride used in the formulations of the present invention surprisingly has a very positive effect on the formation of

nanodispersions. In contrast thereto, the formulations of Weder are polydisperse (see Table 1). In light of the teachings of the Weder reference, this must be regarded as surprising and unexpected. The expert explains why Weder's polydisperse formulations would not be useful for pharmaceutical and cosmetic applications.

The secondary reference, WO 96/37192, discloses pharmaceutical or cosmetic multi-component compositions comprising a) a sphingolipid, (b) a phospholipid, (c) a partial fatty ester, (d) a carrier, (e) a therapeutic agent to be administered (f) a triglyceride and (g) a water-soluble or lipid-soluble additive.

The reference discusses the problems of the low solubility of sphingolipids and glycolipids and the resulting drawbacks for therapeutic and cosmetic uses (see page 2, last paragraph). It teaches to make these important groups of pharmaceutical and cosmetic ingredients available for therapeutic and cosmetic use and to enable the preparation of suitable topical and parenteral dosage forms.

According to the reference it was found that sphingolipids and glycolipids are capable of forming finely dispersed systems having the homogeneity and stability necessary for topical and parenteral dosage forms. This is achieved by dispersing these sparingly soluble substances in combination with phospholipids and a partial fatty ester of polyoxyethylene. The reference does not mention that the triglyceride (component f) is responsible for the solubility-enhancing properties of the sphingolipids and glycolipids, or that this component would improve the ability to form finely dispersed systems.

Component (f) is disclosed in detail starting at the bottom of page 14. No hint is given as to what the function this component is in the composition of this reference. Therefore, one of ordinary skill in the art would not have combined the teaching of the two cited references and added the triglyceride to the formulations of Weder in order to improve the properties of the nanodispersions. The § 103 rejection over the reference combination is therefore unwarranted.

Reconsideration and withdrawal of the rejection of claims 2, 6, 10, 15-21, 24 and 28-29 under 35 U.S.C. § 103(a) as being unpatentable over Weder et al., U.S. Patent 5,997,888 in view of WO 96/37192 is respectfully solicited in light of the remarks *supra*.

Since there are no other grounds of objection or rejection, passage of this application to issue with claims 2, 6, 10, 15-21, 24 and 28-29 is earnestly solicited.

Applicants submit that the present application is in condition for allowance. In the event that minor amendments will further prosecution, Applicants request that the examiner contact the undersigned representative.

Respectfully submitted,

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Enclosure: Declaration

APPENDIX: Marked up version of amended claims.

6 (twice amended). A Method according to claim 28, which is characterised in that the nanodispersion comprises as component

(a) a phospholipid, a hydrated or partially hydrated phospholipid, a lysophospholipid, ~~a ceramide~~ or mixtures thereof.

10 (twice amended). A Method according to claim 28, which is characterised in that the nanodispersion comprises as component (b)

polyethoxylated sorbitan fatty acid esters, polyethoxylated fatty alcohols, polyethoxylated fatty acids, polyethoxylated vitamin E derivatives, polyethoxylated lanolin and ~~the~~ derivatives thereof, polyethoxylated fatty acid partial glycerides, polyethoxylated alkylphenols, ~~sulfuric acid semiesters,~~ polyethoxylated fatty alcohols and ~~the~~ salts thereof, polyethoxylated fatty amines and fatty acid amides~~,~~ and polyethoxylated carbohydrates~~, block polymers of ethylene oxide and propylene oxide~~.

28 (twice amended). A method of preparing a pharmaceutical formulation of a lipophilic pharmaceutical active agent in the form of an aqueous nanodispersion, which steps consist essentially of

(α) mixing the components

(a) 0.1 to 30 % by weight of a phospholipid,

(b) 1 to 50 % by weight of a polyoxyethylene coemulsifier ~~of the polyoxyethylene type~~,

(c) 0.1 to 80 % by weight of a lipophilic component which is a natural or synthetic or a partially synthetic C_4-C_{18}triglyceride, and a lipophilic pharmaceutical active agent, in which any pharmaceutically active agent is lipophilic and is always present as component (c), and

(d) 0.63 to 14.2 % by weight of ethanol

in conventional stirring apparatus until a homogeneous clear liquid is obtained and

(β) adding the liquid obtained in step (α) to ~~the~~ a water phase, wherein (β) is carried out in the absence of high shear or cavitation forces, and wherein the particles in the nanodispersion have an average diameter <50 nm.

29 (twice amended). An aqueous nanodispersion of a lipophilic pharmaceutical active agent, which consists essentially of

(a) 0.1 to 30 % by weight of a phospholipid,

(b) 1 to 50 % by weight of a polyoxyethylene coemulsifier ~~of the polyoxyethylene type~~,

(c) 0.1 to 80 % by weight of a lipophilic component which is a natural or synthetic or a partially synthetic C_4-C_{18}triglyceride, and a lipophilic pharmaceutical active agent, in which any pharmaceutically active agent is lipophilic and is always present as component (c), and

(d) 0.63 to 14.2 % by weight of ethanol, with the proviso that the sum of (a), (b), (c) and (d) is 100 % by weight, plus

(e) a water phase,

which formulation is obtainable by

(α) mixing the components (a), (b), (c), and (d) until a homogeneous clear liquid is obtained, and

(β) adding the liquid obtained in step (α) to athe water phase, wherein step (β) is carried out in the absence of high shear or cavitation forces, and whereby the particles in the nanodispersion have an average diameter <50 nm.